Ghrelin in the Treatment of Catabolic Disorders

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Disclosure

Joseph Gertner, Benjamin Levinson, and Mayumi Furuya are full-time employees of Asubio Pharmaceuticals Inc, USA and Asubio Pharma Ltd, Japan

SUN11031 (synthetic human ghrelin) has not been approved for human use except for research purposes by any regulatory authority in any country
Contents

- Cachexia as a paradigm for catabolic disorders
- What is required of a treatment for cachexia
- Ghrelin as an anti-cachectic therapeutic
- SUN11031 (synthetic human ghrelin) in an animal model of cachexia
- A trial of SUN11031 in COPD-associated cachexia
Cachexia is difficult to define; the definition usually includes a time-dependent (longitudinal) component.

Summary of Definition from Evans et al 2008¹

“Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass”

¹Evans, WJ et al 2008 Clin Nutr 27: 793
Features of Cachexia

Adapted from Evans, WJ et al 2008 Clin Nutr 27: 793
The Impact of Cachexia on the Patient

- Weight loss, principally loss of lean body mass (LBM) and negative protein balance generally
- Functional decline (physical, immunological)
- Increased susceptibility to side-effects of treatment of the underlying condition
- Anorexia
- Depression and decreased quality of life
- Increased morbidity and mortality
- Cachexia as a self-reinforcing cycle
# What Happens in Cachexia

<table>
<thead>
<tr>
<th>Physical appearance of severe disease</th>
<th>Diminished quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>Diminished muscle mass, strength and physical capabilities</td>
</tr>
<tr>
<td>Morbid cycle of cachexia</td>
<td>Lean tissue loss</td>
</tr>
<tr>
<td></td>
<td>Immunity</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Weakness</td>
</tr>
</tbody>
</table>
What is Required of a Treatment for Cachexia?

- Reversal of weight loss
- Restoration of lean body mass
- Improved physical function
- Where the underlying disease is severe and progressive a treatment should at least be able to slow progression of the above
Ghrelin is Anticachectic

- GH release
- Appetite stimulation
- Stimulation of GI motility
- Sympatholytic
- Metabolic rate
- Anticatabolic
- Anti-inflammatory

ANTICACHECTIC

Ghrelin

- Appetite stimulation
- Stimulation of GI motility
- Sympatholytic
- Metabolic rate
- Anticatabolic
- Anti-inflammatory
# Published Trials of Ghrelin in Catabolic States

<table>
<thead>
<tr>
<th>1st Author Reference</th>
<th>Short Title</th>
<th>Number</th>
<th>Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lundholm K</strong>&lt;br&gt;Cancer 2010;116:2044</td>
<td>ghrelin to unselected weight-losing cancer patients</td>
<td>17</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Hotta M</strong>&lt;br&gt;Endocr J. 2009;56:1119</td>
<td>Ghrelin increases food intake in anorexia nervosa</td>
<td>5</td>
<td>N</td>
</tr>
<tr>
<td><strong>Ashby DR</strong>&lt;br&gt;Kidney Int. 2009;76:199</td>
<td>appetite improvement in malnourished dialysis patients</td>
<td>12</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Neary NM</strong>&lt;br&gt;JCEM 2004;89(6):2832</td>
<td>increased energy intake in cancer patients with impaired appetite</td>
<td>7</td>
<td>Y</td>
</tr>
</tbody>
</table>
Effect of Ghrelin on a Cigarette-Smoke Induced Model of COPD
Protocol

Day 1

Exposure to cigarette smoke or air (Sham)
Vehicle, SUN11031 0.1 or 1.0 mg/kg sc, bid

Day 84

Body Weight gain

Grip strength

N=10, Mean ± SE. *** p<0.001 vs. Sham. $$$ p<0.001 vs. Veh.
SUN11031 (Synthetic Human Ghrelin) Improves Lean Body Mass (LBM) and Function in Advanced COPD Cachexia

SUN11031, an investigational drug under development, is a 28 amino acid peptide structurally identical to human ghrelin.
Objectives

• The aim of the present Phase 2 study was to determine whether the administration of SUN11031 could increase body mass and physical performance in cachectic subjects with COPD.
Methods

• 227 eligible male and female subjects age ≥ 50 years with cachexia associated with COPD with FEV₁ 20% to 79% predicted were randomized 1:1:1 to placebo, SUN11031 20 µg/kg and 40 µg/kg bid, all given sc for 84 days.

• The definition of cachexia was based on the consensus statement of Evans et al⁵ with documented involuntary nonedematous weight loss > 5% over 12 months or BMI ≤ 21 kg/m² for males or ≤ 20 kg/m² for females.

• The 6-minute walk test (6MWT) was selected as the 1º endpoint because it is widely used in assessing physical performance in COPD.

• The Short Physical Performance Battery (SPPB), a validated test of lower body function, predictive of morbidity and mortality in middle aged and geriatric subjects, served as a 2º measure of performance.

Plan of Study Treatment Assessments

SUN11031 40 µg/kg BID; 76 subjects
SUN11031 20 µg/kg BID; 75 subjects
Placebo BID; 76 subjects
Efficacy Assessment

• Physical Performance
  - 6 Minute Walk Test
  - Short Physical Performance Battery (SPPB)
  - Handgrip strength
  - Maximum inspiratory pressure

• Body mass
  - Body weight
  - Body composition by dual-energy X-ray absorptiometry (DXA)

• Appetite assessment
  - Appetite assessment by visual analog scale (VAS)

• Safety
  - Standard spirometry
  - Modified MRC dyspnea scale
  - Physical examination
  - Routine biochemistry, endocrine and cytokine biomarkers
Distribution and Disposition of Study Subjects

278 Subjects Screened

- 227 Randomized
  - 224 Safety Population
    - Placebo (n=73)
      - Completed 67 (91.8%)
      - Withdrawn 6 (8.2%)
      - AE* (3)
        - COPD exacerbation (1)
        - Investigator/Sponsor decision (1)
        - Lost to follow-up (1)
    - 20 µg/kg (n=75)
      - Completed 60 (80.0%)
      - Withdrawn 15 (20.0%)
      - AE* (4)
        - COPD exacerbation (3)
        - Withdrawn consent (7)
        - Lost to follow-up (1)
    - 40 µg/kg (n=76)
      - Completed 65 (85.5%)
      - Withdrawn 11 (14.5%)
      - Death (1)
      - AE* (4)
      - Investigator/Sponsor decision (2)
      - Withdrew consent (4)

51 Screen Failures
- AE* (1)
- Inclusion/Exclusion (38)
- Sponsor decision (2)
- Withdrew consent (8)
- Lost to follow-up (2)

* Adverse event (other than exacerbation of COPD)
Demographics (ITT Population, N=214)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=72)</th>
<th>20 µg/kg BID (n=73)</th>
<th>40 µg/kg BID (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>66.1 ± 8.84</td>
<td>64.5 ± 8.05</td>
<td>66.2 ± 9.20</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>67.0 (50-89)</td>
<td>65.0 (51-84)</td>
<td>67.0 (47-86)</td>
</tr>
<tr>
<td><strong>Males, n(%)</strong></td>
<td>41 (56.9%)</td>
<td>51 (69.9%)</td>
<td>48 (69.6%)</td>
</tr>
<tr>
<td><strong>White Race, n(%)</strong></td>
<td>64 (88.9%)</td>
<td>65 (89.0%)</td>
<td>64 (92.8%)</td>
</tr>
<tr>
<td><strong>Hispanic/Latino Ethnicity, n(%)</strong></td>
<td>57 (79.2%)</td>
<td>62 (84.9%)</td>
<td>52 (75.4%)</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>161.48 ± 8.026</td>
<td>164.65 ± 9.520</td>
<td>165.29 ± 7.877</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>162.00 (147.0-179.0)</td>
<td>166.00 (142.2-189.0)</td>
<td>165.00 (150.0-189.0)</td>
</tr>
</tbody>
</table>

SD = standard deviation
## Baseline Characteristics (ITT Population, N=214)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=72)</th>
<th>20 µg/kg BID (n=73)</th>
<th>40 µg/kg BID (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT, meters</td>
<td>317.30 ± 80.616</td>
<td>333.93 ± 78.914</td>
<td>333.30 ± 68.199</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>48.84 ± 7.957</td>
<td>50.63 ± 8.598</td>
<td>53.23 ± 8.812</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>18.65 ± 2.181</td>
<td>18.62 ± 2.278</td>
<td>19.42 ± 2.522</td>
</tr>
<tr>
<td>PI&lt;sub&gt;max&lt;/sub&gt;, cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>48.33 ± 19.118</td>
<td>53.92 ± 30.305</td>
<td>53.87 ± 21.631</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>37.85 ± 6.770</td>
<td>39.25 ± 7.750</td>
<td>40.39 ± 6.801</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>9.28 ± 4.429</td>
<td>9.33 ± 4.859</td>
<td>10.88 ± 5.139</td>
</tr>
<tr>
<td>SPPB</td>
<td>8.7 ± 1.78</td>
<td>9.2 ± 1.91</td>
<td>8.7 ± 2.14</td>
</tr>
</tbody>
</table>

BMI = body mass index; PI<sub>max</sub> = maximal inspiratory pressure  
All data are presented as mean ± standard deviation
No evidence of strength or functional improvement was observed in the intent-to-treat (ITT) population.
Secondary Endpoint: Mean Change from Baseline in Body Weight (ITT)

<table>
<thead>
<tr>
<th>Day</th>
<th>Placebo</th>
<th>SUN11031 20 µg/kg</th>
<th>SUN11031 40 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>29</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>43</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>57</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>85</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>99</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Placebo: 48.84 kg
* SUN11031 20 µg/kg: 50.63 kg
* SUN11031 40 µg/kg: 53.23 kg

* SUN11031 vs Placebo, P < 0.05
** SUN11031 vs Placebo, P < 0.001

Baseline Body Weight (kg)
Placebo: 48.84
SUN11031 20 µg/kg: 50.63
SUN11031 40 µg/kg: 53.23

BL = Baseline; ITT = Intent-to-Treat
Changes in Body Weight and LBM to Day 85

* P < 0.05 vs placebo
** P < 0.001 vs placebo
Secondary Endpoint: Lean Body Mass (ITT)

Baseline Lean Body Mass (kg)
- Placebo: 37.85
- SUN11031 20 µg/kg: 39.25
- SUN11031 40 µg/kg: 40.39

Lean Body Mass Mean Change from BL (kg)

- SUN11031 vs Placebo, P <0.05
- SUN11031 vs Placebo, P<0.001

BL = Baseline; ITT = Intent-to-Treat
Secondary Endpoint: Fat Mass (ITT)

Baseline Fat Mass (kg)
Placebo: 9.28
SUN11031 20 µg/kg: 9.33
SUN11031 40 µg/kg: 10.88

BL = Baseline; ITT = Intent-to-Treat
Responder Analysis of Changes in Body Weight and LBM (ITT Population)

**Responder Analysis: % With Weight Increase**

ITT Population, Day 85 Assessment

<table>
<thead>
<tr>
<th>Weight Gain &gt; 0 kg</th>
<th>Placebo (N=72)</th>
<th>20 μg/kg (N=73)</th>
<th>40 μg/kg (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Subjects</td>
<td>65.3</td>
<td>78.1</td>
<td>85.5</td>
</tr>
<tr>
<td>Weight Gain &gt; 2 kg</td>
<td>25.0</td>
<td>49.3</td>
<td>62.3</td>
</tr>
</tbody>
</table>

**P < 0.01**

**Responder Analysis: % With LBM Increase**

ITT Population, Day 85 Assessment

<table>
<thead>
<tr>
<th>LBM Gain &gt; 0%</th>
<th>Placebo (N=72)</th>
<th>20 μg/kg (N=73)</th>
<th>40 μg/kg (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Subjects</td>
<td>61.8</td>
<td>84.3</td>
<td>85.3</td>
</tr>
<tr>
<td>LBM Gain &gt; 3%</td>
<td>17.6</td>
<td>61.4</td>
<td>58.8</td>
</tr>
</tbody>
</table>

**P < 0.01**
Effect of SUN11031 on Growth Hormone and IGF-1 Concentrations (ITT Population)¹

Sparse sampling was used to obtain GH concentrations, so caution should be used in interpreting GH levels.

¹Sparse sampling was used to obtain GH concentrations, so caution should be used in interpreting GH levels.
In subjects with advanced cachexia, responders were defined as those who experienced both LBM gain and functional improvement. Significantly higher proportion of responders in the SUN11031 treated than in the placebo groups.
Increase in LBM and Improved Performance (Advanced Cachexia Population)

Percentage of Subjects with LBM Increase, by Treatment Group (Advanced Cachexia Population)

Absolute and Percentage Change in SPPB Score (Advanced Cachexia Population with LBM Gain)
## Most Frequently Reported TEAEs
(>5% in Any Treatment Group)

<table>
<thead>
<tr>
<th>Preferred Term, N (%)</th>
<th>Placebo N=73</th>
<th>SUN11031 20 µg/kg bid N=75</th>
<th>SUN11031 40 µg/kg bid N=76</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>23 (31.5)</td>
<td>20 (26.7)</td>
<td>16 (21.1)</td>
</tr>
<tr>
<td>Injection site hematoma</td>
<td>7 (9.6)</td>
<td>3 (4.0)</td>
<td>7 (9.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (6.8)</td>
<td>4 (5.3)</td>
<td>5 (6.6)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>3 (4.1)</td>
<td>6 (8.0)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4 (5.5)</td>
<td>5 (6.7)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (9.6)</td>
<td>2 (2.7)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (1.4)</td>
<td>6 (8.0)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (4.1)</td>
<td>1 (1.3)</td>
<td>5 (6.6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (1.4)</td>
<td>4 (5.3)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2 (2.7)</td>
<td>4 (5.3)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>0 (0.0)</td>
<td>4 (5.3)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (5.5)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (1.4)</td>
<td>0 (0.0)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>0 (0.0)</td>
<td>2 (2.7)</td>
<td>4 (5.3)</td>
</tr>
</tbody>
</table>
Conclusions

- Treatment of subjects with COPD-associated cachexia with the orexigenic and pro-anabolic hormone, SUN11031 at 20 and 40 µg/kg bid resulted in rapid and significant increases in body weight and lean body mass.

- In the ITT population these increases were not associated with improvement in any of the functional performance measures evaluated.

- Selection of subjects with more advanced cachexia who also gained LBM by Day 85, revealed a statistically significant and clinically meaningful increase in performance on the SPPB in subjects receiving 40 µg/kg bid but not 20 µg/kg bid.

- SUN11031 was safe and well-tolerated in both dosage groups. No medically important treatment-related changes were reported in any of the hematology, chemistry, urinalysis, or glucose metabolism parameters, ghrelin antibody levels, or vital signs. Local tolerance of the injections was good.

- The use of a more stringent definition of cachexia and endpoints designed to assess lower body function rather than cardio-respiratory fitness may permit a more accurate assessment of the role of agents designed to treat cachexia in COPD.